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Original Article

Association of circulating suPAR with disease severity and clinical outcomes in patients with ARDS induced by intra-abdominal infections: a prospective observational study

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Abstract: Background: Soluble urokinase-type plasminogen activator receptor (suPAR) is used as a biomarker for inflammatory factor in various conditions, but its potential role as a biomarker in patients with acute respiratory distress syndrome (ARDS) induced by intra-abdominal infection has not yet been assessed. The aim of the current study was to identify the diagnostic and prognostic value of suPAR in this population. Methods: We performed a 1-year prospective observational study in the general intensive care unit of The Affiliated Hospital of Qingdao University, Qingdao, China, from January 2014 to February 2015. Patients who had acquired ARDS as a result of intra-abdominal infection were enrolled into the study, along with patients with sepsis and healthy control individuals. Clinical parameters were recorded and serum samples were collected, and serum levels of suPAR and other inflammatory markers were determined. ARDS patients were followed for 90 days following hospital discharge. Results: A total of 45 ARDS patients, 47 sepsis patients and 50 healthy control individuals were enrolled. ARDS and sepsis patients showed elevated suPAR serum concentrations compared with healthy volunteers, but there were no significant differences between patients with ARDS and those with sepsis. The value of suPAR in the diagnosis of ARDS was therefore limited. However, suPAR levels were associated with ARDS severity and other disease-severity scores, such as Acute Physiology and Chronic Health Evaluation II and the Simplified Acute Physiology Score II. Further analysis revealed that the suPAR level could predict worse outcomes for ARDS patients, and receiver operating characteristic analyses indicated that a suPAR cut-off value of 310 pg/ml on admission was the best predictor of mortality. Kaplan-Meier survival analysis confirmed these results. Conclusions: This prognostic study indicates that suPAR is a reliable marker of ARDS severity and a strong independent predictor of unfavorable outcomes in patients with intra-abdominal infection. However, its power to discriminate between ARDS and sepsis appears to be limited.

Keywords: ARDS, intra-abdominal infection, biomarker, suPAR, prognosis

Introduction

Acute respiratory distress syndrome (ARDS) occurs via a complex process involving inflammation, immunology, coagulation and endothelial dysfunction, but is still not completely understood [1, 2]. Intra-abdominal infection is one of the leading causes of severe sepsis outside of the lungs in intensive care units (ICUs), and often leads to multiple organ dysfunction syndromes such as ARDS and acute renal injury [3, 4]. The early identification of patients at high risk of ARDS would allow physicians to take aggressive treatment measures that might reduce mortality and morbidity [5, 6]. Inflammation biomarkers, such as soluble urokinase-type plasminogen activator receptor (suPAR), may play a pivotal role in the early recognition of sepsis-related ARDS and its appropriate management, and therefore help to save lives [7, 8].

uPAR is expressed on various cell surfaces, including immune cells, endothelial cells, and malignant cells, and is up-regulated and released during inflammation and infection [7, 9].

Table 1. Clinical characteristics of sepsis and ARDS patients at admission to the intensive care unit, and healthy individuals

Characteristic	Healthy controls (n=50)	Sepsis patients (n=47)	ARDS patients (n=45)	*P* value
Men (%)	32 (64.0)	20 (42.6)	29 (64.4)	> 0.05
Age, years	58.1±14.4	62.1±6.4	58.5±14.9	> 0.05
APACHE II score	–	12.3±4.2	19.1±8.0	< 0.01
SAPS II	–	23.8±7.6	39.2±11.4	< 0.01
Etiology				
Intestinal perforation	–	14	10	–
Gastric perforation	–	16	20	–
Appendicitis	–	17	15	–
White blood count ($\times 10^9$)	–	13.2±4.9	15.3±8.0	> 0.05
Lactic acid (mmol/L)	–	1.9±1.1	2.3±1.8	> 0.05
Alanine transaminase (U/L)	–	89.3±24.5	102.8±54.9	> 0.05
Aspartate transaminase (U/L)	–	122.6±37.2	199.7±89.3	< 0.05
CR (umol/L)	–	105.3±25.9	116.8±44.1	> 0.05
Blood urea nitrogen (mmol/L)	–	7.8±2.9	8.8±6.3	> 0.05
High-sensitivity C-reactive protein (mg/L)	–	103.7±29.8	119.5±44.2	< 0.05
Procalcitonin (ng/ml)	–	5.3±8.9	14.2±19.5	< 0.01
SuPAR (pg/ml)	97.4±20.3	232.1±72.0	273.2±97.2	> 0.05

Values are n or mean ± standard deviation. *P* value: ARDS vs. sepsis patients. APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; SAPS, Simplified Acute Physiology Score; suPAR: Soluble urokinase plasminogen activator receptor.

The soluble form of uPAR, namely suPAR, is obtained by cleavage of uPAR from the cell surface. suPAR has been investigated in a variety of conditions and has been shown to have a key role in diagnosis, disease-severity assessment, and prognosis prediction [10-13]. Acute lung injury/ARDS is partly characterized by the accumulation and deposition of extravascular fibrin due to concurrent increased coagulation and decreased fibrinolysis [14, 15]. suPAR is an important mediator involved in the balance of coagulation and fibrinolysis [14]. Therefore, we hypothesized that the clinical manifestation of ARDS might be associated with systematic levels of suPAR. However, the role of suPAR and the relationship between suPAR levels and clinical phenotype in sepsis-related ARDS induced by abdominal infection has, to date, been unclear.

The aims of the current study were to investigate: (1) suPAR expression and its diagnostic value in patients with ARDS induced by intra-abdominal infection; (2) the association between suPAR and other biomarkers of inflammation with respect to disease severity; and (3) whether suPAR, combined with other biomarkers, can improve the prediction of outcomes.

Materials and methods

Study design and patient population

This was a prospective, observational cohort study. The study protocol was approved by the local ethics committee and the study was conducted in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki.

The study was conducted with a large cohort of patients with ARDS induced by intra-abdominal infection who were admitted to the general ICU at The Affiliated Hospital of Qingdao University, Qingdao, China, from January 2014 to February 2015. During the same period, patients with sepsis and intra-abdominal infection, but who did not fulfill the diagnostic criteria for ARDS, were also enrolled. Written informed consent was obtained from each patient, or from the patient's spouse or legal guardian. Patients who were expected to have a short-term (< 48 hours) ICU treatment were excluded.

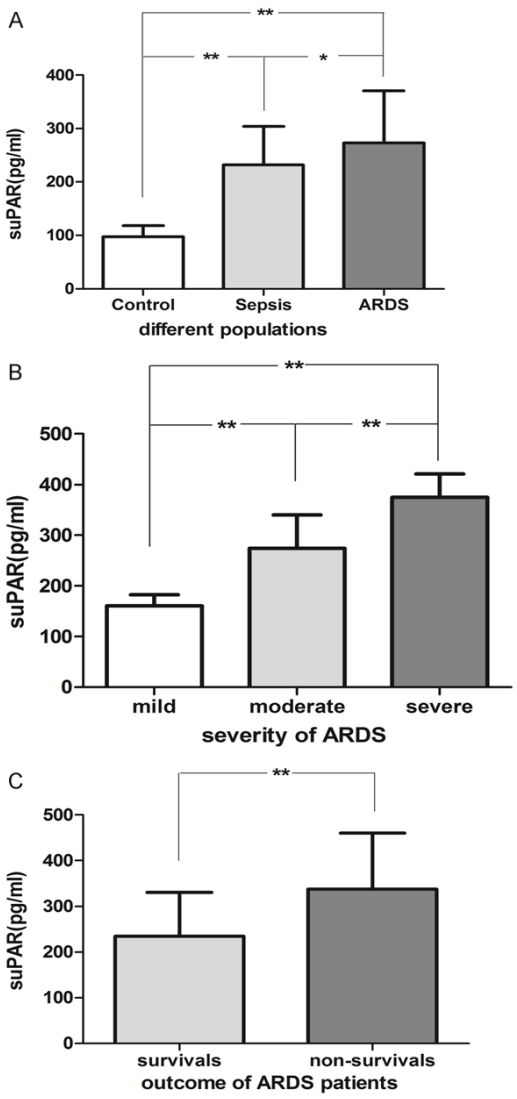

Figure 1. Serum concentrations of soluble urokinase plasminogen activator receptor (suPAR). suPAR levels in: A: Healthy controls, patients with sepsis, and patients with acute respiratory distress syndrome (ARDS); B: Patients with mild, moderate, and severe ARDS; C: Patients with ARDS who survived and those who died. $^{*}P > 0.05$, $^{**}P < 0.05$.

Clinical data

Patient data, clinical information, and blood samples were collected prospectively. Data on patients' characteristics included age, sex, diagnosis, and the origin of the infection. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the Simplified Acute Physiology Score (SAPS) II were calculated on admission to the ICU. Other laboratory parameters were also recorded, including white blood count, platelet count, and liver and renal dysfunction.

Patients were followed after hospital discharge and the survival rate was recorded up to 90 days. The follow-up was conducted through telephone and outpatient interviews by individuals who were blinded to the patient data and research design. During the follow-up period, each patient's clinical course was determined by directly contacting the patient, the patient's relatives, or his/her primary-care physician.

Blood sample collection and detection of serum suPAR and other inflammatory markers

Blood samples were collected upon admission to the ICU. After centrifugation at 3000 rpm for 10 minutes, serum samples were immediately frozen at -80°C for retrospective testing (performed between March and April 2015) with the multiplexed biomarker bundle at the Medical Research Center of The Affiliated Hospital of Qingdao University. The human suPAR serum concentration was detected using a commercial enzyme immunoassay. High-sensitivity C-reactive protein (hsCRP) was measured using immunonephelometry (BN ProSpec II analyzer, Siemens, Germany). Procalcitonin (PCT) was measured using a commercial chemiluminescence immunoassay in a Modular E601 automatic analyzer (Roche Diagnostics, Mannheim, Germany), following the manufacturer's instructions.

Data analysis and statistics

Significance for intergroup differences was assessed using the Fisher's exact or Pearson's Chi-square tests for dichotomous variables, and Student's *t*-test for normally distributed continuous variables. Non-parametric testing was conducted using the Mann-Whitney U-test for variables that did not follow a normal distribution. Receiver operating characteristic (ROC) analysis was used to identify the optimal cut-off value of suPAR to predict 90-day mortality. We also performed Kaplan-Meier curve survival analyses to compare different suPAR levels at admission and clinical outcomes. The Pearson or Spearman correlation coefficient was used to study the correlation between suPAR and other clinical variables such as APACHE II score, SAPS II, and other biomarkers, including hsCRP and PCT. A P value of < 0.05 was considered

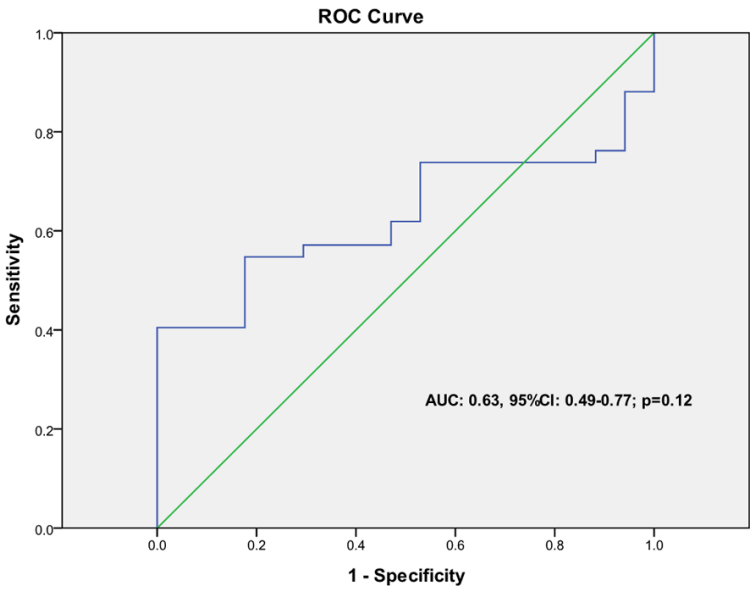

Figure 2. Receiver operating characteristic (ROC) analysis of the power of soluble urokinase plasminogen activator receptor (suPAR) on the day of admission to diagnose patients with ARDS (acute respiratory distress syndrome).

Table 2. Plasma suPAR levels on admission according to severity of ARDS

	Mild (n=12)	Moderate (n=17)	Severe (n=16)	*P* value
suPAR, pg/ml	160.9±22.4	274.5±66.2	374.5±47.0	< 0.01

Values are mean ± standard deviation. *P* value: severe vs. mild and moderate ARDS. Statistical significance was assumed for $P < 0.05$. ARDS, acute respiratory distress syndrome; suPAR, soluble urokinase plasminogen activator receptor.

statistically significant. All analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline data and patient characteristics

A total of 92 patients were enrolled in our study (49 men and 43 women; median age 60.3 years, range 25-82 years; **Table 1**). Overall, 45 of these patients had bacterial sepsis from the abdominal cavity and met the diagnostic criteria for ARDS, as proposed by the Berlin definition [1]. Sepsis patients (n=47) met the criteria of sepsis proposed by the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Committee for severe sepsis and septic shock [3], but did not have ARDS. As a further control population, we analyzed data from 50 healthy blood donors with normal suPAR values.

Value of SuPAR in the diagnosis of ARDS

Both ARDS and sepsis patients displayed a strongly significant increase in serum suPAR compared with the healthy control group. However, there was no significant difference in suPAR serum concentrations between the ARDS and sepsis patients (**Table 1** and **Figure 1A**). To test the power of suPAR to diagnose ARDS, we performed ROC analyses of suPAR and other classic inflammatory parameters. The obtained curves indicated that the area under the ROC curve (AUC) for suPAR (AUC 0.61, 95% confidence interval [CI] 0.49-0.75 **Figure 2**) was lower than that for hsCRP (AUC 0.65, 95% CI 0.42-0.67) and PCT (AUC 0.72, 95% CI 0.56-0.81).

Correlation between suPAR or other biomarkers and ARDS severity

Serum suPAR concentrations increased with the severity of ARDS, presenting a linear relationship. Significant differences were found among all three groups (i.e., mild, moderate, and severe ARDS, according to the Berlin criteria of ARDS severity; **Figure 1B** and **Table 2**). Tukey's test indicated that suPAR levels in patients with severe ARDS were significantly higher than those in patients with moderate or mild disease (**Table 2**).

We compared the serum levels of suPAR with the major inflammatory and infectious markers (i.e., hsCRP and PCT) and disease-severity scores (i.e., APACHE II and SAPS II). The mean suPAR level for all ARDS patients was 273.2±97.2 pg/ml, which was related to hsCRP (r=0.254, $P < 0.01$), PCT (r=0.35, P= 0.02), APACHE II score (r=0.57, $P < 0.01$), and SAPS II (r=0.62, $P < 0.05$).

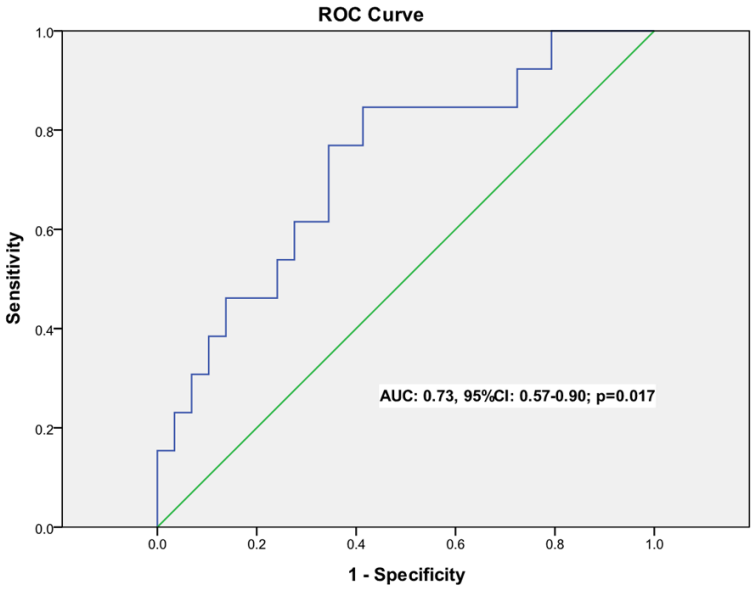

Figure 3. Receiver operating characteristic (ROC) analysis of the power of soluble urokinase plasminogen activator receptor (suPAR) on the day of admission to predict 90-day mortality in patients with acute respiratory distress syndrome.

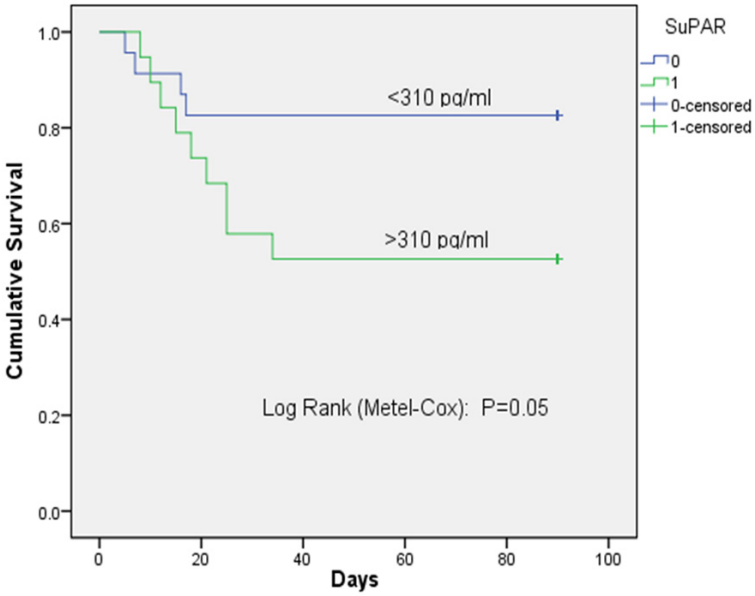

Figure 4. Kaplan-Meier survival analysis. *P*atients with ARDS who had a soluble urokinase plasminogen activator receptor (suPAR) level of > 310 pg/ml on admission had a lower probability of survival than those with a suPAR level of < 310 pg/ml.

Association between suPAR and ARDS patient endpoints

In ARDS patients, suPAR levels on the day of admission were significantly higher in those who died within 90 days compared with those who survived (341.8 vs. 242.8 pg/ml, respectively, *P*=0.004; **Figure 1C**). ROC analyses indicated that a cut-off suPAR value of 310 pg/ml on the day of admission was the best predictor of 90-day mortality (AUC 0.78, 95% CI 0.63-0.93; sensitivity 0.69, specificity 0.65; **Figure 3**). Finally, Kaplan-Meier survival analysis was conducted to compare the time to death (up to 90 days of follow-up) for ARDS patients with an admission suPAR level of > 310 vs. < 310 pg/ml. Log-rank (Mantel-Cox) testing indicated that patients in the > 310 pg/ml group had a significantly shorter survival rate than those in the < 310 pg/ml group (X^2=3.61, *P*=0.05; **Figure 4**).

Discussion

This study, from a homogeneous patient population with abdominal infection and ARDS, firstly revealed that ARDS as well as sepsis patients had elevated suPAR serum concentrations compared with healthy volunteers, but that there were no significant differences between patients with ARDS and those with sepsis without ARDS. We can therefore infer that suPAR has limited value in diagnosis. The suPAR level was also associated with the severity of ARDS and with other disease-severity scores, such as APACHE II and SAPS II. Further analysis revealed the suPAR level at ICU admission could predict outcomes for ARDS patients. ROC analyses indicated that a suPAR cut-off value of 310 pg/ml on admission was the best predictor of mortality. Kaplan-Meier survival analysis confirmed these findings.

suPAR is derived from proteolytic cleavage of and release from cell-membrane-bound uPAR

[16]. suPAR is involved in inflammation, modulation of cell adhesion, cell migration, and cell proliferation through a plasminogen-activating pathway [9]. Coagulation and fibrinolysis play vital roles in the mechanisms of acute lung injury/ARDS, and activation of coagulation is both a consequence of and contributor to ongoing lung injury [14]. suPAR, as a receptor in the hematological system, has been defined not only as a key biomarker, but also as a mediator of a variety of processes, including the immune response, coagulation, fibrinolysis, and inflammation [8].

Various observational studies and systemic reviews have revealed that suPAR, as a non-specific marker of inflammation, has low diagnostic value [8]. A systemic review conducted by Backes and colleague revealed that the area under the ROC curve for suPAR in predicting which patients would develop sepsis was poor (AUC 0.62, 95% CI 0.51-0.72) [8].

The plasma levels of suPAR positively correlated with the severity of ARDS, which might eventually help to triage patients with severe ARDS. Risk stratification and prediction of unfavorable outcomes can be used to make decisions on the need for a patient to remain in the ICU admission or transfer to a more general department. Previous studies have demonstrated that suPAR can predict disease severity in patients with bacteremia or ventilator-associated pneumonia [17-19].

Leukocytes and the vascular endothelium might be the main sites of suPAR production [20, 21]. The membrane-bound form of uPAR has been shown to facilitate the phagocytosis of bacteria and apoptotic neutrophils, while suPAR has been shown to inhibit neutrophil efferocytosis [22]. Therefore, cleavage of uPAR might reflect a functional impairment in the host's defenses, rather than being a surrogate marker for inflammation. Impaired engulfment has been associated with poor outcomes in preclinical models of sepsis, which might explain the greater prognostic value of suPAR [23]. In the current study, suPAR levels were significantly higher in ARDS patients who died vs. those who survived, which is in accordance with previous findings in critically ill patients [24-26]. APACHE II, SAPS II, and other scoring systems estimating the risk of mortality have become popular in the field of ARDS research [27]. suPAR has a similar prognostic ability to other, established scoring systems. Several studies in various situations have shown that an increase in suPAR levels indicates an unfavorable prognosis. For example, Koch and colleagues reported that circulating suPAR levels were stably elevated during the first week of treatment and could predict mortality in critically ill patients [24]. In a prospective cohort study that enrolled 539 emergency-room patients with suspected infection, a high suPAR level remained an independent predictor of mortality after adjusting for potential confounders [26]. Recent studies have also identified an elevated level of plasma suPAR as an independent predictor of poor outcomes in patients with suspected or known coronary artery disease and those experiencing an out-of-hospital cardiac arrest [13, 28].

This study has three main limitations. Firstly, the study involved too few participants and had a too-short duration of follow-up, which might have restricted the study's efficacy. Secondly, some of the patients with abdominal infections might have had gastroenteric tumors, which could have affected the suPAR level. Finally, our analysis did not measure suPAR levels over the disease course and during follow-up, including after full recovery and discharge from hospital.

In conclusion, our results indicate that suPAR can be used as a biomarker of severity and to predict the outcomes of patients with ARDS induced by abdominal infection. Further studies are advocated to explore the value of suPAR in treatment and predicting response to treatment.

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Disclosure of conflict of interest

None.

Authors' contribution

Liang Shan and Yun-Bo Sun designed the study, analyzed data, and wrote the manuscript. Jing Li performed the suPAR measurements. Feng Shan and Xiu Li collected clinical data, assisted in patient recruitment, and performed follow-up. Feng Shan also assisted with statistical analyses.

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